Hormones and endometrial cancer—new data from the Million Women Study

In this week's *Lancet*, investigators from the Million Women Study (MWS) report important results on the extensively studied but incompletely understood relation between menopausal hormones and risk of endometrial cancer. Most epidemiological studies focus on oestrogens alone, which are used mainly by hysterectomised women. For women with an intact uterus, present formulations involve combined oestrogen-progestagen therapy, on the basis of findings that progestagens counteract the proliferative effects of unopposed oestrogens on endometrial tissue.[1] However, there are several unresolved questions, including how progestagens should be prescribed and the effects of extended use.[2]

The MWS provides the most extensive data yet to address these questions. By comparison with never using hormones, continuous combined therapy was associated with reduced risk, cyclical combined therapy with no alteration in risk, and oestrogens alone with increased risk. The study also provides unique data on tibolone, a drug that is available in certain areas of Europe, but not in the USA. Tibolone was associated with significant increases in the risk of endometrial cancer, in a manner similar to unopposed oestrogen therapy, leading to a need for cautious clinical use. Although observational in nature and not a clinical trial, the study's extensive data enabled adjustment for a wide variety of other lifestyle factors.

In addition to allowing an evaluation of the effects of different formulations and regimens, the design of the MWS enabled an assessment of hormone effects according to characteristics of the users. Thin women are more likely to use hormones than heavier women, who face higher risks of developing endometrial cancer.[3] Thus, of particular interest is whether hormonal risks differ according to the users' anthropometric characteristics. In the MWS, relative risks for all formulations were highest in thin women. Continuous or cyclical combined therapy was associated with substantially reduced risks in obese women, whereas tibolone led to substantially increased risks in normal and overweight women.

A full understanding of clinical implications requires consideration of relative risks, which compare cancer rates in exposed individuals (eg, exogenous hormone users) with rates in unexposed women (eg, never users), and absolute risks of disease incidence. The MWS responsibly provided both. The absolute risks emphasise the importance of obesity as a major predictor of the risk of endometrial cancer, but this pertained mainly to individuals who were not exposed to exogenous hormones. There was no gradient in risk with obesity in users of continuous combined therapy. The MWS shows that any benefits for endometrial cancer associated with continuous combined therapy are far outweighed by risks for breast cancer, which is adversely affected by this therapy. The absolute risks also remind us of the need to consider multiple disease outcomes when balancing risks and benefits.

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A limitation of the MWS was that women were followed up, on average, for only 3·4 years. Of concern for endometrial cancer are recent data suggesting that long-term use of continuous combined therapy might carry increased risks compared with non-use.[4] It is therefore noteworthy that the MWS showed that the risk for users of 5 years or more approximated that of never users. Additional follow-up of women in this study will be important for clarifying effects of long-term use. However, given the complex and dynamically changing nature of hormonal use, other studies will be needed to fully understand the spectrum of effects.

Stephen Wood

Although for years it was believed that hormones would reduce risk for various diseases, well-designed randomised trials have failed to substantiate these claims.[5–8] Hormones effectively reduce the risk of fractures, but do not reduce the risk of most coronary, cerebrovascular, and cognitive events. There is also accumulating evidence that hormones might increase the risk of ovarian cancer, although reductions in the risk of colorectal cancer seem probable.[6]

Hormones clearly remain the most effective therapy for menopausal symptoms, their original indication when first marketed.[9] Thus the important clinical question is how hormones can be prescribed in a fashion that will allow women to receive the greatest benefits without commensurate risks. To minimise cancer and other risks, clinicians should prescribe the lowest possible dose of oestrogen for short periods of time.[10,11] Fortunately, recent evaluations support the idea that oestrogens prescribed at low doses (eg, 0·3 mg a day conjugated equine oestrogen) are generally as effective in controlling menopausal symptoms as the traditional higher doses.[12]

The million dollar—or pound or euro—question is: how long can women stay on hormones without adverse effects? Although the benefits of short-term use of hormones during the perimenopausal period appear to outweigh risks,[13] how should patients be counselled as the time from menopause progresses? Given that women face various physiological changes as they age, other approaches for symptom relief and disease prevention must be found to replace the role once filled by hormone pills.[9] Oestrogens given locally can alleviate urogenital symptoms, whereas vaginal lubricants might improve sexual activity. Some antidepressants, including serotonin and norepinephrine reuptake inhibitors, provide moderate relief from hot flashes. Regular physical activity, both cardiovascular and weight-bearing, can maintain cardiovascular health, preserve strong bones, and ward off obesity's many adverse health outcomes. A balanced and moderate diet, supplemented by calcium (1500 mg a day) and vitamin D (400–600 IU daily), will prevent osteopenia and osteoporosis (which may also be reduced by biphosphonate therapy). Regular use of aspirin might be warranted for cerebrovascular health. Continued mental vigour appears to decrease the risk of Alzheimer's disease. But for women whose menopausal symptoms persist, chronic oestrogen (with or without a progestagen) might be required. For these women and their clinicians, continued research on the long-term risks and benefits of hormone therapy, screening modalities, and effective risk communication remains an important priority.

Louise A Brinton, James V Lacey Jr, Edward L Trimble
National Cancer Institute, Bethesda, MD 20892, USA
brinton@nih.gov

We declare that we have no conflict of interest.

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Still looking for answers in COPD

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Despite rapid developments in our understanding of the pathophysiology of chronic obstructive pulmonary disease (COPD),[1] clinical progress in outcomes that matter to patients, such as survival, shortness of breath, and exacerbations, has been slower. In today's *Lancet*, the result of the Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) is another example of this disappointing trend. Rennard wrote that two major problems facing clinicians treating patients with stable COPD are underdiagnosis and a nihilistic attitude.[2] I might add a third—ineffective therapy.